Results of Drug Treatment of Patients with Metastasis of Triple Negative Breast Cancer

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ABSTRACT

Triple negative breast cancer (TNBC) is characterized by the absence of estrogen receptors (ER), progesterone receptors (PR) and HER-2/neu expression. TNBC is a heterogeneous disease with an aggressive course, with a high risk of early local and distant metastasis to the visceral organs and/or brain. Relapse usually occurs between the 1st and 3rd years, and most patients die within 5 years of the initial diagnosis. Studies have shown that young women predominate among patients with TNBC. Triple negative breast cancer is often associated with BRCA mutations, especially when diagnosed at a young age. Chemotherapy remains the main treatment for patients with TNBC due to the lack of specific drug targets (hormone receptors or HER-2 amplification). However, at present there are no uniform standards for the treatment of patients with TNBC metastases. An important task remains the further study of new regimens and drug regimens for patients with generalized triple-negative breast cancer, which can improve the immediate and long-term results of their treatment.

Keywords: triple negative breast cancer, metastases, chemotherapy

Currently, breast cancer is one of the five most common cancers in the world and is the leading cause of death for women under the age of 50. Detection of breast cancer during preventive examinations throughout the country remains low, and the rate of neglect IIIB - IV stage, which is the leading criterion for the quality of diagnosis, on the contrary, is high. [1]. Over the past decade, the concept of breast cancer has changed. Breast cancer is a heterogeneous disease with different pathogenic pathways and includes several unique and distinct subtypes. For many decades, the TNM classification of breast cancer has been used all over the world, which reflects the quantitative characteristics of the tumor, the size of the primary lesion, the number of regional metastases and the presence of distant metastases [2,3]. To some extent, these quantitative characteristics reflected the biological tumor grade. With the development of molecular genetic research, several biologically distinct forms of this disease have been identified. This classification has become actively used in the clinic to personalize treatment and study new methods of therapy [5]. For every 1 million detected cases of breast cancer, more than 170 thousand are triple-negative breast cancer (TNBC) [6]. The phenomenon of the “paradox of triple negative breast cancer” describes the high sensitivity of TNBC to chemotherapy, despite an unfavorable prognosis in general [7]. Currently,

chemotherapy is the main method of treatment for patients with TNBC, but there are no uniform standards for choosing a treatment regimen. Triple-negative breast cancer is characterized by a predominance of visceral metastasis, including the lungs (p=0.01) and the brain (p=0.035), less often - metastasis only to the bones, which occurs mainly in luminal subtypes of breast cancer (p=0.0031) , and HER-2-overexpressed tumors more often metastasize to the liver (p=0.17) [8]. We have developed and proposed for clinical practice a new drug treatment regimen using bevacizumab, oxyloplatin and docetaxel for patients with metastases of triple-negative breast cancer. Intratumoral expression of VEGF and proliferative activity of tumor cells are much higher in patients with triple negative breast cancer than in patients with other tumor variants, which provides a biological justification for the use of angiogenesis inhibitors for the treatment of patients with TNBC [9]. Thus, the use of a chemotherapy regimen with bevacizumab proved to be effective in the treatment of patients with metastases of triple-negative breast cancer [9]. Oxaliplatin is an antitumor agent, a platinum derivative, capable of rapidly interacting with DNA, forming intra- and interhelix cross-links, which blocks its synthesis and subsequent replication [11]. Complete, partial, overall response and disease control rates were 3.8; 30.8; 34.6 and 69.2% respectively. The median follow-up time was 13.7 months. The median disease-free survival time was 6.7 months. (95% CI, 4.5–9.0), and the median overall survival (OS) was 13.3 months. (95% CI, 9.1–17.5) [12]. In addition, oxaliplatin does not fully cross-resistance with cisplatin or carboplatin and remains effective in some cases of cisplatin or ant resistance. raciclines [10]. Thus, we propose this regimen of anticancer therapy for use in clinical practice.

The aim of the work is to improve the immediate and long-term results of treatment of patients with TNBC metastases by using a new drug treatment regimen that includes bevacizumab, oxaliplatin and docetaxel; comparing its effectiveness with such schemes as TAC, FAC, "cisplatin + paclitaxel"; evaluation of the results of treatment of the regimen "bevacizumab + oxaliplatin + docetaxel" when prescribed in the first lines of therapy.

Materials and methods. The study included 52 patients with triple negative breast cancer. The diagnosis of cancer was confirmed by histological and immunohistochemical methods. The median age was 54 (28–76) years. Prior to inclusion of patients in our study, all 62 patients underwent neoadjuvant chemotherapy. Of these, 12/62 (19.4%) patients received preoperative chemotherapy according to the AC regimen, 14/62 (22.6%) - according to the "carboplatin + docetaxel" regimen, 15/62 (24.1%) - according to the paclitaxel regimen. + carboplatin, 21/62 (38.9%) patients - according to the AC scheme, then chemotherapy with paclitaxel + carboplatin. Surgical treatment was performed in all patients. Madden mastectomy was performed most frequently - 45 (86.5%) of 52 patients. 5 (9.6%) patients underwent mastectomy according to Pati, two (3.8%) patients underwent radical resection. Neoadjuvant treatment of patients was carried out between 2014 and 2016. In addition, all patients also received radiation therapy. After the manifestation of the progression of the disease, the patients underwent a comprehensive examination, including: clinical research methods; laboratory research methods (general blood test, biochemical blood test, blood test for the CA 15-3 tumor marker, urinalysis, histological and immunohistochemical examination of the primary tumor and regional metastases); methods of visualization of metastases (ultrasound, bone scintigraphy, CT, MRI, PET-CT, radiography). The timing of disease progression was counted from the end of primary treatment for detected breast cancer (neoadjuvant chemotherapy, surgical treatment, radiation therapy - according to indications) and until the appearance of distant metastases. When assessing the timing of progression, it was noted that they ranged from 2 to 181 months, the median was 21.8 months. In a quarter of patients, generalization of the process was detected within a period of 9.8 months. (first year of observation), another

quarter - after 37.7 months. (after three years of observation).

At the first stage, for chemotherapy with various studied schemes, the patients (n=62) were randomly distributed into four groups. Group I included 16 patients, group II - 15, group III - 15, group IV - 16 patients. As the results of the examination of patients from all four groups showed, the defeat of one organ was observed quite rarely. Thus, metastatic lesions of the lungs in the groups ranged from 4.5 to 19%, bones - from 4.5 to 20%, damage only to the liver was observed in 5% of cases. Most often there was a multiple lesion of various organs and tissues. In particular, the frequency of diagnosing metastases to the lungs and liver in the groups was from 4.5 to 5.0%, metastasis to the lungs and bones - from 4.5 to 8.7%, metastatic lesions of the lungs, skin and soft tissues - from 4 .8 to 8.7%, metastasis to the lungs and distant lymph nodes - from 4.3 to 18.2%, metastatic lesions of the liver, skin and soft tissues - from 4.8 to 5.0%, liver and distant lymph nodes - 4 .8%, lungs and brain - 5.0%, Multiple combined metastatic lesions of bones, skin and soft tissues were diagnosed in groups in 8.7% of cases. Metastases to the skin, soft tissues and distant lymph nodes were detected with a frequency of 4.8 to 18.2%. Multiple combined lesions of the lungs, liver, bones occurred in 4.3% of cases in groups. Metastases to the lungs, liver, lymph nodes were diagnosed by groups in 4.8% of patients. Combined metastatic lesions of the lungs, bones and lymph nodes were observed in 4.3% of cases. Metastases to the lungs, skin, soft tissues and lymph nodes were diagnosed by groups with a frequency of 4.3 to 9.1%. Combined damage to the liver, bones, skin and soft tissues was detected in 4.3% of cases in groups. Metastases to the liver, bones and distant lymph nodes were diagnosed in 5.0% of patients from group III. Combined metastatic lesions of the liver, skin, soft tissues and brain were diagnosed in 4.3% of the groups. Multiple metastatic lesions of the lungs, bones, skin, soft tissues and lymph nodes were detected in 4.5% of cases in group II and in 5.0% in group III. Thus, the groups were comparable in terms of the number of patients and the location and combination of metastases of triple-negative breast cancer in them ($p<0.5$)

Research results. In group I (16 patients), as the first line of palliative chemotherapy for metastases of triple-negative breast cancer, a regimen previously not used in clinical practice was prescribed with the inclusion of bevacizumab 10 mg/kg, oxaliplatin 75 mg/m2 intravenously by drip in 1- day and docetaxel 75 mg/m2 intravenously drip on the 2nd day (interval between courses - 3 weeks). The number of courses ranged from 4 to 8. In 66.7% of cases, 6-8 courses of chemotherapy were performed, in 33.3% - 4 courses. The assessment of the immediate therapeutic effect was carried out after 2, 4, 6 and subsequent courses of chemotherapy. Data on the therapeutic effect of the chemotherapy regimen with the inclusion of bevacizumab, oxaliplatin and docetaxel are presented in Table. 1.

Table 1. Immediate effect of first-line chemotherapy (bevacizumab, oxaliplatin and docetaxel) n=16

Therapeutic effect	**Number of patients**	**P**
Full	5/16 (31,3%)	p<0,05
Partial	7/16 (43,7%)	p<0,05
Stabilization	3/16 (18,7%)	p<0,05
Progression	1/16 (6,3%)	p<0,05

The duration of remission varied from 5 to 13 months with a full effect, and from 1 to 7 months with a partial effect. The median time to progression was 8 months for full effect and 3.4 months for partial effect. Of the toxic reactions during chemotherapy according to the "bevacizumab + oxaliplatin + docetaxel" regimen, neurotoxicity of stage 1-2 was noted - 76.2% of patients, neutropenia of stage 3-4 - 9.5%, thrombocytopenia of stage 1 - 4.8%, anemia 1-2 - 23.8%, nausea / vomiting - 4.8% of the patient. The toxicity of the proposed regimen, taking into account strict adherence to drug doses (oxaliplatin 75 mg/m2, docetaxel 70

mg/m2) and the number of chemotherapy courses (maximum 6-8 courses followed by maintenance injections of bevacizumab 10 mg/kg No. 3), was acceptable, the treatment was well tolerated by patients, not there was a need to reduce doses or cancel chemotherapy.

15 patients included in group II were prescribed chemotherapy according to the TAC scheme: docetaxel 75 mg/m2 intravenously by drip (day 1), doxorubicin 60 mg/m2 by intravenous bolus (day 1), carboplatin AUC 4 intravenously by drip (day 1) . The interval between courses is 3 weeks. The number of courses ranged from 2 to 7. In 45.5% of cases, 6 courses were performed. After TAC chemotherapy for triple negative breast cancer metastases, the immediate effect was evaluated.

Table 2. Immediate effect of first line TAC

Therapeutic effect	Number of patients	P
Full	2/15 (13,3%)	p<0,05
Partial	3/15 (20,0%)	p<0,05
Stabilization	6/15 (40,0%)	p<0,05
Progression	4/15 (26,7%)	p<0,05

The duration of remission varied from 5 to 6 months with a full effect, and from 1 to 17 months with a partial effect. It should be noted that the threshold for the duration of partial remission at 19 months. reached only one patient, which is explained by the initial lesion of only one area (metastases to distant lymph nodes). The median time to progression with full effect was 4.6 months, and with partial effect it was 5.8 months. Taking into account compliance with the intervals between chemotherapy courses and doses of drugs, the tolerability of chemotherapy according to the TAC regimen was acceptable. Of the toxic reactions during the use of chemotherapy according to the TAC scheme, neutropenia 1-2 st - 22.7%, 3-4 st - 9.1%, thrombocytopenia 1 st - 22.7%, anemia 1-2 st - 36.4 %, nausea/vomiting stage 1-2 - 40.9% of patients.

In group III, all 15 patients received first-line chemotherapy according to the FAC scheme: cyclophosphamide 500 mg/m2 intravenously by drip (day 1), doxorubicin 50 mg/m2 by intravenous drip (day 1), 5-fluorouracil 500 mg/m2 by intravenous drip (1st day). The interval between courses is 3 weeks. The number of courses ranged from 6 to 8. The immediate effect of treatment according to the FAC scheme is presented in Table. 3. In group III, in most cases, after first-line chemotherapy according to the FAC scheme, disease progression was diagnosed, the full effect was not achieved in any patient.

Table 3. Immediate effect of first line FAC

Therapeutic effect	Number of patients	P
Full	0/15 (0,0%)	p<0,05
Partial	2/15 (13,3%)	p<0,05
Stabilization	3/15 (20,0%)	p<0,05
Progression	10/15 (66,7%).	p<0,05

Only 13.3% of patients had partial regression of the tumor. The duration of remission fluctuated with a partial effect from 1 to 8 months. The median duration of response to treatment was 4.5 months. Of the toxic reactions during chemotherapy according to the FAC scheme, neutropenia of stage 1–2 was noted - 25% of patients, thrombocytopenia of stage 1 - 10% of patients, anemia of stage 1–2 - 20% of patients, nausea / vomiting of stage 1–2 - 60% of patients . When prescribing in group II chemotherapy according to the TAC scheme and in group III chemotherapy according to the FAC scheme, the total dose of anthracyclines was taken into account - the maximum dose of doxorubicin did not exceed the recommended 500 mg/m2. Patients were treated under strict

hematological control. Blood tests were done at least once a week.

In group IV, 16 patients received chemotherapy according to the TR scheme: paclitaxel 135 mg/m2 intravenously by drip (day 1), cisplatin 75 mg/m2 by intravenous drip (day 2). The interval between courses is 3 weeks. In most cases (47.8%), 6–8 courses of chemotherapy were performed, 4 courses were administered to seven patients (30.4%). The immediate effect is presented in table. 4.

Table 4. Immediate effect of first-line chemotherapy according to TR regimen

Therapeutic effect	**Number of patients**	**P**
Full	3/16 (18,7%)	p<0,05
Partial	4/16 (25,0%)	p<0,05
Stabilization	2/16 (12,5%)	p<0,05
Progression	7/16 (43,7%)	p<0,05

The duration of remission ranged from 3 to 8 months. The median duration of response was 3.5 months. Of the toxic reactions during chemotherapy according to the TR scheme, neutropenia of 1–2 tbsp was noted. in 12/23 (52.2%) patients, neutropenia 3-4 st - 21.7%, thrombocytopenia 1 st - 30.4%, anemia 1-2 st - 56.5%, 3-4 st - 8, 7%, nausea/vomiting stage 1-2 - 78.3% of patients. Analysis of the obtained results revealed differences in the effectiveness of treatment with different chemotherapy regimens among the four groups.

As can be seen from the data, in group I, after antitumor therapy according to the scheme "bevacizumab + oxaliplatin + docetaxel", an improvement in the results of direct efficacy was noted compared with the other three groups. Progression-free survival was assessed after first-line chemotherapy in four compared groups. Differences in relapse-free survival rates were noted among the groups (p=0.09), while group I showed a prolongation of remission after the first line of chemotherapy according to the "bevacizumab + oxaliplatin + docetaxel" regimen. The median duration of response to treatment during chemotherapy according to the scheme "bevacizumab + oxaliplatin + docetaxel" with a full effect was 7 months, with a partial effect - 3.4 months. With other regimens, the median time to progression ranged from 1.6 months to 1.6 months. with a partial effect in group IV up to 4.6 months. with full effect and 5.8 months. with partial effect for group II patients. Patients who were diagnosed with the progression of the process at the first stage after using the first-line chemotherapy with four regimens were prescribed individual chemotherapy, taking into account previous treatment, the general condition of the patient and the prevalence of the disease. We analyzed the overall survival of patients with metastases of triple-negative breast cancer, which was calculated from the start of the first-line chemotherapy of one of the four study regimens (bevacizumab + oxaliplatin + paclitaxel, TAC, FAC, TP) to the death of patients in four study groups .

Discussion. Triple negative breast cancer is an aggressive tumor subtype with a high risk of disease progression, early damage to internal organs and the central nervous system. Given the significant molecular heterogeneity, an interesting direction in the development of drug therapy for TNBC metastases is the study of regimens that are atypical for the treatment of other subtypes of breast cancer. As can be seen from the presented results, drug treatment using the new regimen "bevacizumab + oxaliplatin + docetaxel" showed high efficiency in the treatment of patients with metastases of triple-negative breast cancer. This study demonstrates a general trend towards improved outcomes in the treatment of TNBC metastases with the use of new antitumor therapy regimens that are not typical for other BC subtypes. Comparison of the effectiveness of other commonly used first-line chemotherapy regimens for TNBC metastases, such as TAC, FAC and TR, did not show any advantage over the drug regimen introduced into clinical practice. The toxicity of the bevacizumab, oxaliplatin, and docetaxel regimen was

acceptable, and the treatment was well tolerated by patients. Improvement in progression-free survival was obtained in group I (p = 0.08), where after the first line of chemotherapy four patients remained in remission (with a follow-up period of 12 to 20 months), which is 15–20% higher than in the other three groups .

Literature

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